



# DEMENTIA NEWSLETTER *for* PHYSICIANS

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## Clinical Trials in Alzheimer Disease



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Alzheimer disease (AD) is a fatal disorder for which we have no cure, and few treatments. It is an inexorably progressive neurodegenerative disorder which eventually affects all brain functions. In its earlier stages it primarily affects thinking; including memory, and language,

attention and personality. It continues to progress, until the person is no longer able to independently take care of their basic daily needs, such as eating, and voiding. Eventually, the person with AD will die, usually due to complications of the disease, such as infections and clots.

Currently, we have medications available in Canada for the treatment of AD: the acetylcholinesterase inhibitors and memantine. As we have come to understand, through the initial pivotal clinical trials and our own clinical use of these medications, these medications are invaluable in the treatment of AD. Unfortunately, these medications affect only the symptoms of the disease, and do not affect the underlying disease process.

The precise mechanism(s) responsible for AD is/are unknown. The most compelling contemporary hypothesis for the neuronal loss and cognitive decline in AD is the amyloid hypothesis, which states that AD is the result of amyloid overproduction and/or ineffective clearance. It maintains that accumulation of Ab peptide in the brain is the critical step in the pathogenesis of AD and that slowing or halting the accumulation of Ab in the brain, or aiding its removal from the brain will slow, halt, or potentially even reverse the course of the disease.

Most of the current and upcoming clinical trials are aimed at decreasing the brain amyloid 'load'. It is hoped that decreasing the amount of brain amyloid will result in either slowing down or possibly even stopping the underlying disease process in AD.

### 1. Anti-Amyloid Vaccination Studies

This is the most promising area of research in recent years. Initially, active vaccination with Ab in mouse models of AD showed extraordinary results on both tests of cognition and in terms of amyloid plaque clearance in

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sacrificed animals. This vaccination was taken in to trials with humans. Unfortunately, there was an approximately 6% rate of encephalitis, which did result in serious complications in some of the participants. Despite this, there was a marked reduction of plaque seen in the few patients that have now come to autopsy.

Since that time, investigators have been looking for a way to make vaccination safer. The main way that this has been done is through passive immunization with monoclonal antibodies to different parts of the amyloid molecule, or active immunization with fragments of amyloid. Currently, these trials are going very well. They are now generally in phase 2 or phase 3, including some very large phase 3 trials which are ongoing.

### 2. Medications that decrease production of Amyloid

Various medications have tried this in different ways over the last number of years, using a variety of different approaches. One current medication in phase 3 trials is a gamma synthetase inhibitor. Gamma synthetase is one of the enzymes responsible for synthesis of A- $\beta$ . A recent trial of an anti inflammatory agent, probably working as a gamma synthetase inhibitor, (r-flurbiprofen) was negative.

### 3. Medications to increase clearance

Recently Neurochem, (a Montreal company), had a medication that interfered with the fibrillization and oligomerization of A- $\beta$ , thus decreasing the ability of it to form plaques. Unfortunately, the clinical trial did not come out positive.

There are also a number of other new, possibly disease modifying medications coming to late-phase clinical trials.

#### 1. Dimebon

This medication is a medication that was used primarily as a cold medicine in Eastern Europe and Russia. It was found serendipitously to have a possibly disease modifying effect on AD. Its mechanism of action in AD is interesting: it is thought to work through a mitochondrial mechanism. A large clinical trial in North America, where it will be added on to cholinesterase inhibitors, will start soon.

#### 2. Rember

This medication is now in phase 2 trials. It is an anti-tau medication, and is showing promise as a disease modifying medication in AD. By its mechanism, it should also have some effect on other dementias, such as Fronto-temporal dementia.

In addition to disease modifying medications, companies are also trying to make better/more efficient symptomatic medications, and some of these are now at the phase 2/3 level as well.

The Ottawa Dementia Research Unit is an Academic Clinical Trials Unit, located at Elisabeth Bruyère Hospital. We are associated with the Memory Disorder Clinic, Bruyère Continuing Care, and University of Ottawa. We are endorsed by the Alzheimer Society of Ottawa and Renfrew County, and the Champlain Dementia Network. We are currently recruiting for a number of clinical trials, and are looking for patients with Alzheimer's Disease. If you have a patient that you think would be interested and suitable for one of our trials, or wish more information, please call us at 613-562-6328.